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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,669	MARLIERE ET AL.	
	Examiner	Art Unit	
	Gerald G. Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 1/28/2005, in which the remainder of the pending claims were cancelled and new claims were added (claims 86-118). Claims 86-118 are pending in the instant application and are under consideration.

Any rejection of record in the previous office action not addressed herein is withdrawn. This action is not final due to new grounds of rejection that are made herein that were not necessitated by applicants' amendment of the claims in the response filed on 1/28/2005.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 86-118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment of the claims in the response filed on 1/28/2005.**

The rejected claims have been amended to specify that the cells obtained in part (a) are cultured in a medium that (1) lacks a nutrient compensating for the loss of function of a mutated, essential protein for the host cell, and which (2) contains an unconventional amino acid that restores the functionality of the protein required for growth of the cells, the unconventional

amino acid being any amino acid incorporated in place of the amino acid which would normally be incorporated at the site with regard to the translated nucleic acid sequence. First, there is no clear and positive prior antecedent basis for the phrase "the amino acid which should normally be incorporated at this site with regard to the translated nucleic acid sequence", making it unclear whether the amino acid residue that "should normally be incorporated at this site" refers to the one encoded by the unmutated essential gene or the one encoded by the missense mutation at the target codon. In any case, the claim recites a particular set of culture conditions that are broader in scope than what is described in the specification. Namely, the claim as amended encompasses embodiments where the selection is done based on the incorporation of any noncanonical amino acid at the site. The response does not point to any particular section of the originally filed specification and/or claims for support for this particular selection step. Nor does there appear to be support for claiming the selection step using any noncanonical amino acid other than the one normally encoded by the target codon. Therefore, the added limitation is impermissible New Matter.

Claims 86-118 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments where the target cells are grown in selective conditions where the culture medium 1) does not comprise the nutrient required by the loss of functionality of the mutated protein of step (a), 2) further comprises the amino acid encoded by the target codon prior to its alteration in step (a) and wherein the cells capable of growth in the culture conditions are selected, does not reasonably provide enablement for embodiments lacking this specific selection step. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This is a new rejection made on the basis that several of the claims are directed to selection of cells having a specific property, but which don't actually recite a selection step. This rejection is also necessitated in part by applicants' amendment of the claims to broadly recite that the culturing/selection step can be done with literally any amino acid.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The nature of the invention is complex, involving the use of selection pressures to select cells comprising a mutation that allow the cell to incorporate unconventional amino acids. The claimed methods utilize a missense mutation in a gene encoding an essential protein for a target cell to select for cells that acquire the ability to compensate for the loss of the function of the essential protein. The claims encompass embodiments where such selection pressure is not applied. The specification describes experiments where cells modified to include missense mutations in an essential gene are grown in defined media (e.g. minimal media) in the presence of large quantities of an amino acid encoded by the original target codon of the essential protein (i.e. prior to the incorporation of the missense mutation), where the selective media does not comprise a nutrient whose requirement is necessitated by the missense mutation of the essential protein. The working examples are solely directed to embodiments where selective pressure is

applied by culturing in defined media 1) lacking a nutrient required by the mutation of the essential protein, and 2) in the presence of the amino acid encoded by the target codon prior to its alteration to a missense codon. In each of the working examples, applicants were able to demonstrate a mutation in the aminoacyl-tRNA synthetase corresponding to the missense codon which allows the mutated aminoacyl-tRNA synthetase to incorporate amino acids other than the one specified by the missense codon (e.g. the amino acid encoded by the original target codon or other, non-canonical amino acids such as aminobutyrate). The specification teaches two working examples wherein the mutated aminoacyl-tRNA synthetase obtained via their selection methods apparently has increased ability to incorporate non-canonical amino acids such as L-2-aminobutyrate or L-3-thiol-2-aminobutyrate (e.g. Examples 6-7). However, no teachings or working examples are provided for embodiments lacking this selection pressure. No rational is provided for how one would expect to obtain mutants allowing incorporation of such unconventional amino acids in the absence of the cited selection pressure (i.e. absence of the required nutrient and presence of the original amino acid).

The methods described in the specification appear to be novel in the art. Therefore, there is no teaching in the prior art to offset the cited deficiencies of the instant specification. Because no rational is provided in the instant specification or prior art for practicing embodiments of the claimed invention in the absence of selection pressure applied by culturing the cells in the presence of the amino acid encoded by the original target codon and in the absence of the essential nutrient necessitated by alteration of the target codon, it would be unpredictable to attempt to practice the claimed methods in the absence of such selection pressure. Therefore, it

would take undue, trial-and-error experimentation of an unpredictable nature to practice the claimed methods in the full broad scope encompassed by the rejected claims.

Claims 103-105 & 107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection similar to the grounds of rejection made in the previous office action, mailed 7/24/2004 and repeated below.**

The rejected claims are drawn to host cells obtained by methods of selection wherein a missense mutation is incorporated into a an essential gene required for growth of the host cell and the cell is grown under selective conditions wherein 1) the culture medium does not contain a nutrient that will compensate for the lack of a functional copy of the essential gene product, and 2) the culture medium contains an amino acid not encoded by the missense mutation and which will restore functional activity when incorporated into the mutated protein. Claims 69, 71-72 and 74 encompass any mutant of any gene that will compensate for the loss of the essential gene product. For example, loss of an essential drug resistance marker might be compensated for by the generation of a "leaky" mutant of a protein pump on the cell surface. Thus, rejected claims 69, 71-72 and 74 encompass a number of different mutants that do not necessarily include mutants of a tRNA-synthase gene corresponding to the missense codon and which would differ depending upon the nature of the essential gene. The instant specification and prior art appear to only describe embodiments wherein a mutant tRNA synthase gene is identified that can

incorporate a non-canonical amino acid into an essential protein and do not provide a basis to envision what other types of mutations might occur in a cell that compensate for the loss of a given essential protein. Further, the instant specification and prior art do not clearly describe what mutations in what functional domains of different aminoacyl-tRNA proteins will allow the mutated aminoacyl-tRNA synthetase to function in the manner recited in the rejected claims (e.g. for claim 70 which does actually recite the presence of a mutated aminoacyl-tRNA synthetase in the claimed cell).

Response to Arguments/112 1st Rejection

Applicant's arguments filed on 4/21/2004 have been fully considered but they are not persuasive. The response essentially argues that the amendment of the claims obviates the outstanding grounds of rejection. The response further argues that applicants' method encompasses embodiments where the tRNA-synthetase gene is not necessarily the altered gene that confers an ability to grow under the selective conditions (e.g. other genes involved in protein synthesis could be involved.

Applicants' arguments actually support and are consistent with the grounds of rejection provided above. The examiner agrees that there is no explicit limitation in the rejected claims that the mutation which confers the desired property of being able to incorporate noncanonical amino acids is the mutation in the aminoacyl-tRNA synthetase and that other mutations could account for the observed growth under selective conditions. This is a large part of the examiner's argument that the genus of isolated cells encompassed by the rejected claims is huge and that applicants have not provided a basis for the skilled artisan to envision those embodiments that meet the functional limitations of the claims. Further, applicants' response

does not address the need to provide a structural/functional basis for the skilled artisan to envision those embodiments that are limited to mutations in an aminoacyl-tRNA synthetase. What are the primary nucleic acid sequences for the mutations obtained in the instant application? Can one extrapolate from these mutations to envision other mutated aminoacyl-tRNA synthetase genes that will confer the required functional activity? The specification and prior art do not provide a basis for the skilled artisan to envision such embodiments and, therefore, there is no basis for the skilled artisan to envision a sufficient number of specific embodiments to describe even the genus of mutations that are limited to aminoacyl-tRNA synthetase genes.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 86-118 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections.**

Claim 86 is vague and indefinite in that there is no clear and positive prior antecedent basis for the phrase "the amino acid, which should normally be incorporated at this site with regard to the translated nucleic acid sequence". Does the phrase refer to the amino acid residue encoded by the missense mutation or to the one encoded by the target codon prior to the incorporation of the missense mutation?

Claim 108 recites the phrase "selecting a cell by a method according to Claim 97". It is unclear whether one must practice the active methods steps of claim 97 or not. For example,

would one satisfy the claim limitation by practicing a similar method "according to" claim 97? It would be remedial to amend the claim language to clearly indicate that the selection is done by the method of claim 97 so that it is clear that the active steps recited in claim 97 are necessarily performed in practicing the method of claim 108.

Similarly, claim 118 recites the limitation of "wherein said incorporation is obtained according to the process of Claim 108". It would be remedial to amend the claim to recite that the incorporation of the unconventional amino acid comprising a functional group is done according to the method of claim 108.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G. Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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